[0006] Covalent modification of histones is a fundamental mechanism of control of gene expression, and one of the major epigenetic mechanisms at play in eukaryotic cells (Kouzarides, *Cell*, *128*, 693-705 (2007)). Because distinct transcriptional states define fundamental cellular processes, such as cell type specification, lineage commitment, cell activation and cell death, their aberrant regulation is at the core of a range of diseases (Medzhitov *et al.*, *Nat. Rev. Immunol.*, *9*, 692-703 (2009); Portela *et al.*, *Nat. Biotech.*, 28, 1057-1068 (2010)). A fundamental component of the epigenetic control of gene expression is the interpretation of histone modifications by proteins that harbor specialized motifs that bind to such modifications. Among them, bromodomains have evolved to bind to acetylated histones and by so doing they represent fundamental links between chromatin structure and gene transcription (Fillipakoppoulos *et al.*, *Cell*, *149*, 214-231 (2012)).

[0007] Bromodomains, which are approximately 110 amino acids long, are found in a large number of chromatin-associated proteins and have been identified in approximately 70 human proteins, often adjacent to other protein motifs (Jeanmougin F., et al., *Trends Biochem. Sci.,* 1997, *22*, 5, 151-153; and Tamkun J.W., et al., *Cell*, 1992, *7*, 3, 561-572). Interactions between bromodomains and modified histones may be an important mechanism underlying chromatin structural changes and gene regulation. Bromodomain-containing proteins have been implicated in disease processes including cancer, inflammation and viral replication. *See, e.g.*, Prinjha *et al.*, *Trends Pharm. Sci.*, 33(3):146-153 (2012) and Muller *et al.*, *Expert Rev.*, 13(29):1-20 (September 2011).

[0008] Cell-type specificity and proper tissue functionality requires the tight control of distinct transcriptional programs that are intimately influenced by their environment. Alterations to this transcriptional homeostasis are directly associated with numerous disease states, most notably cancer, immuno-inflammation, neurological disorders, and metabolic diseases. Bromodomains reside within key chromatin modifying complexes that serve to control distinctive disease-associated transcriptional pathways. This is highlighted by the observation that mutations in bromodomain-containing proteins are linked to cancer, as well as immune and neurologic dysfunction. Hence, the selective inhibition of bromodomains across the family creates varied opportunities as novel therapeutic agents in human dysfunction.

[0009] There is a need for treatments for cancer, immunological disorders, and other bromodomain related diseases.

SUMMARY

[00010] In one example, the present invention refers to use of a CBP/EP300 bromodomain inhibitor in the manufacture of a medicament for treating or delaying progression of cancer in an individual. In ~~One aspect~~ one example, ~~of the present invention is~~ there is disclosed a method for treating cancer in an animal comprising administering an effective amount of a CBP/EP300 bromodomain inhibitor to the animal.

[00011] ~~One aspect of the present invention is~~In one example, there is disclosed a method for treating or delaying progression of cancer in an individual comprising administering an effective amount of a CBP/EP300 bromodomain inhibitor to the individual.

[00012] In one aspect, the present invention refers to use of a CBP/EP300 bromodomain inhibitor in the manufacture of a medicament for enhancing immune function in an individual having cancer, the use comprising an effective amount of a CBP/EP300 bromodomain inhibitor to be administered to the individual. In one example, there is disclosed ~~One aspect of the present invention is~~ a method of enhancing immune function in an individual having cancer comprising administering an effective amount of a CBP/EP300 bromodomain inhibitor.

[00013] In certain ~~embodiments~~examples, CD8 T cells in the individual have enhanced priming, activation, proliferation and/or cytolytic activity relative to prior to the administration of the CBP/EP300 bromodomain inhibitor.

[00014] In certain ~~embodiments~~examples, the number of CD8 T cells is elevated relative to prior to administration of the CBP/EP300 bromodomain inhibitor.

[00015] In certain examples~~embodiments~~, the CD8 T cell is an antigen-specific CD8 T cell.

[00016] In certain examples~~embodiments~~, the cancer has elevated levels of T-cell infiltration.

[00017] In certain examples~~embodiments~~, the cancer is associated with increased intratumoral Treg cell density.

[00018] In certain examples~~embodiments~~, the cancer is selected from acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes, embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, head and neck cancer, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer (NSCLC), oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer, and Wilms' tumor.

[00019] In certain ~~embodiments~~examples, the cancer is melanoma, NSCLC, renal, ovarian, colon, pancreatic, hepatocellular, or breast cancer.

[00020] In certain examples~~embodiments~~, the cancer is NSCLC, ovarian, pancreatic, hepatocellular, or breast cancer.

[00021] In certain examples~~embodiments~~, the cancer is melanoma, NSCLC, or renal cell carcinoma.

[00022] In certain examples~~embodiments~~, the CBP/EP300 bromodomain inhibitor inhibits CBP.

[00023] In certain examples~~embodiments~~, the CBP/EP300 bromodomain inhibitor inhibits EP300.

[00024] In certain examples~~embodiments~~, the method suppresses Treg function.

[00025] In certain examples~~embodiments~~, the method decreases T cell exhaustion of $CD8^+$ T cells.

[00026] In certain examples~~embodiments~~, the CBP/EP300 bromodomain inhibitor does not bind to the HAT domain of CBP and/or EP300.

[00027] In certain examples~~embodiments~~, the individual is a human, e.g., a female or male.

[00028] One aspect of the present invention is a CBP/EP300 bromodomain inhibitor for use in medical treatment or diagnosis including therapy and/or treating cancer.

[00029] One aspect of the present invention is a method for selecting an anti-cancer compound, comprising determining whether a test compound is a CBP/EP300 bromodomain inhibitor compound, wherein a test compound that is a CBP/EP300 bromodomain inhibitor compound is selected as an anti-cancer compound.

[00030] In certain examples~~embodiments~~, the methods disclosed herein further comprise, determining whether the test compound binds to the HAT domain of CBP and/or EP300, wherein a test compound that does not bind to the HAT domain of CBP and/or EP300 is selected as an anti-cancer compound.

[00031] In certain examples~~embodiments~~, the method further comprises determining whether the test compound suppresses Treg function, wherein a test compound that suppresses Treg function is selected as an anti-cancer compound.

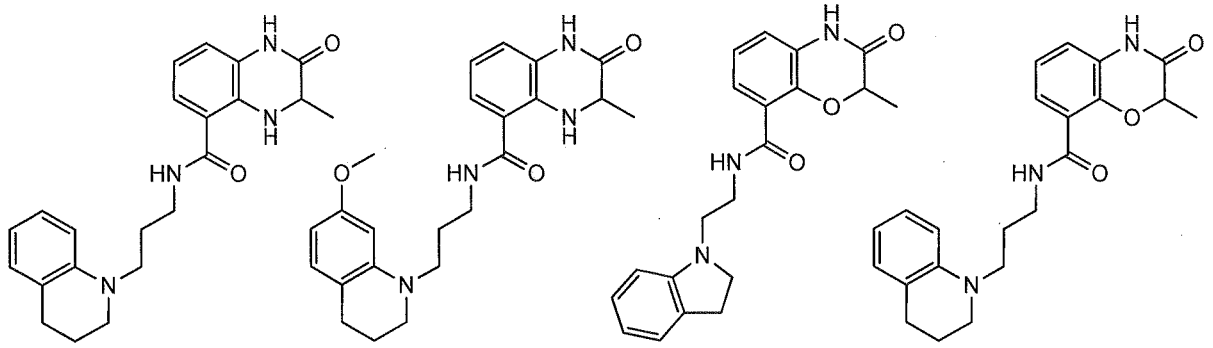
[00032] In certain examples~~embodiments~~, the method further comprises determining whether the test compound decreases T cell exhaustion of $CD8^+$ T cells, wherein a test compound that decreases T cell exhaustion of $CD8^+$ T cells is selected as an anti-cancer compound.

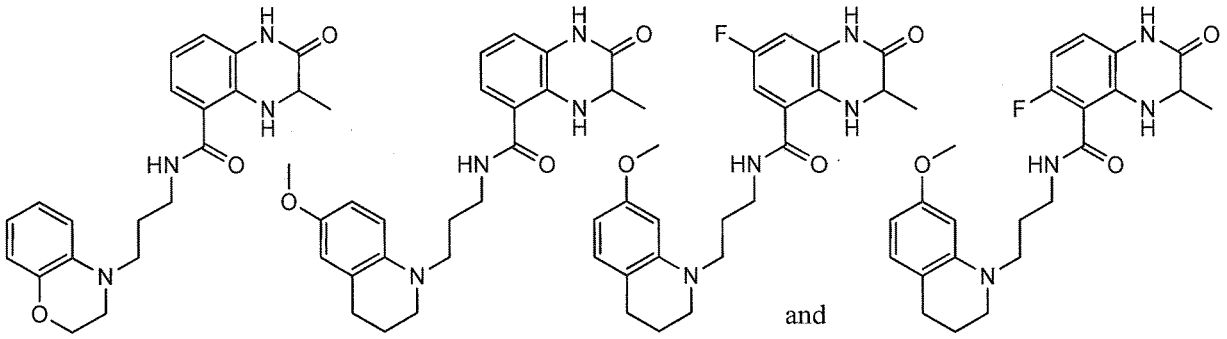
[00033] In certain examples~~embodiments~~, the CBP/EP300 bromodomain inhibitor compounds may include compounds of Formula I, an isomer or a mixture of isomers thereof (e.g., enantiomers) or a pharmaceutically acceptable salt, solvate or prodrug thereof. Such compounds, and processes and intermediates that are useful for preparing such compounds, are described in *Angew. Chem. Int. Ed.*, 2014, v53, pages 1-6 and corresponding supporting information. In some ~~embodiments~~examples, the compounds of Formula I include:

R_8 independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, and OC_1-C_6 alkyl;

or a salt thereof.

[00034] In certain ~~examplesembodiments~~, the compound of Formula I is selected from the group consisting of:





and ;

or a salt thereof.

BRIEF DESCRIPTION OF THE FIGURES

[00035] Figure 1. Human naïve T cells were cultured under Treg-differentiating conditions in the presence of active compound targeting the bromodomains of CBP/EP300, or inactive control compound. As depicted in Figure 1, the CBP/EP300 inhibitor CBP/EP300(1), but not the inactive compound CBP/EP300(A), reduced the number of FOXP3+ cells generated, as seen by flow cytometry.

[00036] Figure 2. Dose-response curves were determined with two exemplar active compounds from distinct chemical scaffolds, CBP/EP300(1) and CBP/EP300(2). These active compounds, but not the inactive ones, CBP/EP300(A) and CBP/EP300(B), reduced the number of FOXP3+ cells in a dose-dependent manner (Figure 2, upper panels). The activation marker CD25 was not affected by any compound treatment, suggesting that these cells are functional, although unable to differentiate into the Treg lineage (Figure 2, lower panels).

We claim:

1. Use of a CBP/EP300 bromodomain inhibitor in the manufacture of a medicament~~A method~~ for treating or delaying progression of cancer in an individual~~ comprising administering an effective amount of a CBP/EP300 bromodomain inhibitor to the individual~~.

2. Use of a CBP/EP300 bromodomain inhibitor in the manufacture of a medicament for~~A method of~~ enhancing immune function in an individual having cancer~~ comprising administering an effective amount of a CBP/EP300 bromodomain inhibitor to the individual~~.

3. The ~~method~~ use of claim 1 or 2, wherein CD8 T cells in the individual have enhanced priming, activation, proliferation and/or cytolytic activity relative to prior to the administration of the CBP/EP300 bromodomain inhibitor.

4. The ~~method~~ use of claim 3, wherein the number of CD8 T cells is elevated relative to prior to administration of the CBP/EP300 bromodomain inhibitor.

5. The ~~method~~ use of any one of claims 3-4, wherein the CD8 T cell is an antigen-specific CD8 T cell.

6. The ~~method~~ use of any one of claims 1-5, wherein the cancer has elevated levels of T-cell infiltration.

7. The ~~method~~ use of any one of claims 1-6, wherein the cancer is associated with increased intratumoral Treg cell density.

8. The ~~method~~ use of any one of claims 1-7, wherein the cancer is selected from acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes, embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, head and neck cancer, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer (NSCLC), oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer,

pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer, and Wilms' tumor.

9. The ~~method~~ use of any one of claims 1-8, wherein the cancer is melanoma, NSCLC, renal, ovarian, colon, pancreatic, hepatocellular, or breast cancer.

10. The ~~method~~ use of any one of claims 1-9, wherein the cancer is NSCLC, ovarian, pancreatic, hepatocellular, or breast cancer.

11. The ~~method~~ use of any one of claims 1-8, wherein the cancer is melanoma, NSCLC, or renal cell carcinoma.

12. The ~~method~~ use of any one of claims 1-11, wherein the CBP/EP300 bromodomain inhibitor inhibits CBP.

13. The ~~method~~ use of any one of claims 1-11, wherein the CBP/EP300 bromodomain inhibitor inhibits EP300.

14. The ~~method~~ use of any one of claims 1-13, wherein the method suppresses Treg function.

15. The ~~method~~ use of any one of claims 1-14, wherein the method decreases T cell exhaustion of $CD8^+$ T cells.

16. The ~~method~~ use of any one of claims 1-15, wherein the CBP/EP300 bromodomain inhibitor does not bind to the HAT domain of CBP and/or EP300.

17. The ~~method~~ use of any one of claims 1-16, wherein the individual is a human.

18. A CBP/EP300 bromodomain inhibitor for use in medical treatment or diagnosis including therapy and/or treating cancer.

19. A method for selecting an anti-cancer compound, comprising determining whether a test compound is a CBP/EP300 bromodomain inhibitor compound, wherein a test compound that is a CBP/EP300 bromodomain inhibitor compound is selected as an anti-cancer compound.

20. The method of claim 19, further comprising determining whether the test compound binds to the HAT domain of CBP and/or EP300, wherein a test compound that does not bind to the HAT domain of CBP and/or EP300 is selected as an anti-cancer compound.

21. The method of claim 19 or 20, further comprising determining whether the test compound suppresses Treg function, wherein a test compound that suppresses Treg function is selected as an anti-cancer compound.